RESPONSE

I. Status of the Claims

Prior to the Action, claims 4-10, 23-27, 41 and 49-68 were pending. In light of restriction issues, examination has focused on claims 4-10, 23-27, 41, 49, 50, 57-59, 61-65 and 68, and claims 51-56, 60, 66 and 67 are said to be withdrawn from consideration (see **Section V** for details). Claims 4, 6, 7, 27, 49, 50, 63 and 68 are subject to rejection, and claims 5, 8-10, 23-26, 41, 57, 58, 61, 62, 64 and 65 are objected to as dependent on a rejected base claim, but are otherwise allowable (see **Section II** for details). Claim 59 is not accounted for in the Action (see Action at summary page, and page 3).

Presently, allowable claim 10 has been cancelled without prejudice or disclaimer and claim 4 has been amended, without prejudice or disclaimer, to include the language of allowable claim 10. Overall, claims 4, 50, 63 and 66 have been amended without prejudice or disclaimer. Claims 69-82 have been added, of which claims 69-81 are based upon other allowable claims. The new claims are fully supported by the application as filed and unified with the examined claims.

Claims 4-9, 23-27, 41 and 49-82 are therefore in the case. According to 37 C.F.R. § 1.121(c), a copy of the pending claims is provided in the amendment section.

II. Allowed Claims

Applicants appreciate the Action's determination that many claims are allowable (Action at summary page, and page 7). In particular, that claims 5, 8-10, 23-26, 41, 57, 58, 61, 62, 64 and 65 are each allowable, although "objected to" as dependent on a rejected base claim (Action at summary page, and page 7).

Without acquiescing with any rejection in any way, Applicants presently elect to place most claims in immediate condition for allowance by acting upon the Action's indication of allowable claims. Accordingly, independent claim 4 has been amended to incorporate the language of allowable dependent claim 10, thus placing claim 4 into allowed form. All claims directly or indirectly dependent on claim 4 are also now in allowed form. Although many of these claims were themselves allowable (Action at summary page, and page 7), claims 6, 7, 27, 49, 50 and 63 (formerly rejected) and claims 51-56, 60, 66 and 67 (said to have been withdrawn, see **Section V**) are now in allowed form, based on the Action's determination that claim 10 is allowable.

New claims 69-81 are also in immediate condition for allowance, being independent claims separately based upon allowable dependent claims 5, 8, 9, 23, 25, 26, 41, 57, 58, 61, 62, 64 and 65, respectively.

Thus, according to the Action's determination of allowable claims, claims 4-9, 23-27, 41, 49-67 and 69-81 are now unquestionably in allowed form. The present response shows that the two remaining claims, claims 68 and 82, are also in condition for allowance.

III. Support for the Claims

Support for the revised and new claims is to be found throughout the specification and claims of the original and parent applications. The small entity fees necessary for the new claims should be deducted from Williams, Morgan & Amerson, P.C. Deposit Account No. 50-0786/4001.002299.

Claim 4 has been amended to include the language of allowable claim 10, and is supported throughout the specification and by allowable claim 10 in particular.

Claim 50 has been revised to add the agent carmustine, which is supported by the specification, in particular by Table B.

Claims 63 and 66 have been amended to delete the phrase "at a biologically effective time", thus making claims 63 and 66 more consistent with claims 4, 62 and 68. The amendments are supported throughout the specification as exemplified by claims 4, 62 and 68.

New claim 69 is an independent claim based upon allowable dependent claim 5, and is supported throughout the specification and by allowable claim 5 in particular.

New claim 70 is an independent claim based upon allowable dependent claim 8, and is supported throughout the specification and by allowable claim 8 in particular.

New claim 71 is an independent claim based upon allowable dependent claim 9, and is supported throughout the specification and by allowable claim 9 in particular.

New claim 72 is an independent claim based upon allowable dependent claim 23, and is supported throughout the specification and by allowable claim 23 in particular.

New claim 73 is an independent claim based upon allowable dependent claim 25, and is supported throughout the specification and by allowable claim 25 in particular.

New claim 74 is an independent claim based upon allowable dependent claim 26, and is supported throughout the specification and by allowable claim 26 in particular.

New claim 75 is an independent claim based upon allowable dependent claim 41, and is supported throughout the specification and by allowable claim 41 in particular.

New claim 76 is an independent claim based upon allowable dependent claim 57, and is supported throughout the specification and by allowable claim 57 in particular.

New claim 77 is an independent claim based upon allowable dependent claim 58, and is supported throughout the specification and by allowable claim 58 in particular.

New claim 78 is an independent claim based upon allowable dependent claim 61, and is supported throughout the specification and by allowable claim 61 in particular.

New claim 79 is an independent claim based upon allowable dependent claim 62, and is supported throughout the specification and by allowable claim 62 in particular.

New claim 80 is an independent claim based upon allowable dependent claim 64, and is supported throughout the specification and by allowable claim 64 in particular.

New claim 81 is an independent claim based upon allowable dependent claim 65, and is supported throughout the specification and by allowable claim 65 in particular.

Finally, new claim 82 is a separate independent claim based upon claim 4 prior to the present amendment, which is supported throughout the specification and by claim 4 in particular.

It will therefore be understood that no new matter is included within any of the amended or new claims.

IV. Rejection of Claims 4, 27, 49 and 68 for Double-Patenting

Claims 4, 27, 49 and 68 are rejected under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 4, 27-29, 42, 47 and 68 of U.S. Patent No. 6,406,693 ("the '693 patent"; Attorney Docket No. 4001.002200).

In response, Applicants presently submit a Terminal Disclaimer and the new small entity fee.

Applicants stress that the six-way restriction requirement and the § 103(a) rejection, to the extent that it applies to claims 68 and 82, are *prima facie* improper in light of the obviousness-type double-patenting rejection over the '693 patent. As independent claim 4 in the present application is not patentably distinct from claims 28 and 29 in the '693 patent, and as the

'693 claims are patented (*i.e.*, drawn to a single, non-obvious invention), the present claims must also be drawn to a single, patentable invention.

V. Restriction Issues

A restriction requirement was earlier set forth, taking the position that original claims 4-10, 23-27, 41 and 49-68 were drawn to six allegedly distinct inventions, wherein administering the second therapeutic agent gave rise to the distinct inventions. No reasoning was given to support the position that the inventions were "distinct". Applicants traversed on various grounds. The Action is unpersuaded, and makes the restriction final (Action at pages 2-3). Applicants maintain their traversal on the grounds provided earlier and set forth below.

A. Examination and Allowance in the Present Application

Initially, Applicants point out that the continued withdrawal of claims 52, 60, 66 and 67 is *prima facie* improper based upon the history of the present application alone.

In particular, withdrawn claim 52 defines the therapeutic agent as angiostatin or endostatin. Angiostatin and endostatin are included within claim 65, which the Action has examined and found allowable. Claim 52 is thus properly joined with the examined claims and allowable on the same grounds as the Action examined and allowed claim 65.

Withdrawn claim 60 defines the therapeutic agent as a calcium ionophore. Calcium ionophores are included within claim 65, which the Action has examined and found allowable. Claim 60[1] is thus properly joined with the examined claims and allowable on the same grounds as the Action examined and allowed claim 65[1].

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[1]Claim 59, which is not accounted for in the Action, defines the therapeutic agent as a calcium-flux inducing agent. Calcium-flux inducing agents are included within claim 65, which the Action has examined and found allowable. Claim 59 is thus properly joined with the examined claims and allowable on the same grounds as the Action examined and allowed claim 65.

Withdrawn claims 66 and 67 each depend from claim 62, which the Action has examined and found allowable. Claims 66 and 67 are therefore properly joined with the examined claims and allowable on the same grounds as the Action examined and allowed claim 62s.

B. Other Evidence, Including Issued Patents

Claims 52, 60, 66 and 67 are properly joined with the examined claims and allowable according to examination of this application, as set forth above. The other withdrawn claims are also properly joined with the examined claims on various grounds.

Applicants earlier pointed out that the restriction requirement in the present application was in contradiction with earlier decisions of the Office, particularly in the parent application that issued as the '693 patent. In the '693 patent, the Office held that the treatment of cancer by administering an anti-aminophospholipid antibody and **any** second anti-cancer agent was a unified invention not properly subject to restriction.

The Action bridging pages 2-3 quotes the text of the respective issued and pending claims, but does not explain *s* the combined administration of any second anti-cancer agent is a unified invention in the '693 patent, but that narrower claims constitute six different inventions in the present application. Moreover, the Action's reasoning in fact supports Applicants' position.

In particular, the Action at page 3 quotes the '693 patent as claiming the combined administration of chemotherapeutic, radiotherapeutic, anti-angiogenic and apoptosis-inducing agents. At the very least, it is therefore clear that claims drawn to the combined administration of chemotherapeutic, radiotherapeutic, anti-angiogenic and apoptosis-inducing agents must be examined together. With reference to the present application, withdrawn claims 51 (and 52), must therefore be included with the other examined claims.

The foregoing evidence leaves only claims 53-56, of original Groups III, IV and V, for further discussion. The only reasoning in the Action to support the ongoing restriction is that each of an inflammatory cytokine, H_2O_2 and thrombin "are distinct their [*sic*] mechanism of action and also, chemical structure" (Action at page 3).

Firstly, Applicants respectfully point out the claims are not directed to compounds in which the chemical structures are important, or even to methods in which the chemical structures of the compounds form the basis of search, examination or patentability. Rather, all the claims are drawn to treating cancer by administering an anti-aminophospholipid antibody, already found to be patentable in the '693 patent, and simultaneously or sequentially administering a second anti-cancer agent, already found to be patentable in the '693 patent, where the second anti-cancer agent is further defined as in the pending claims.

Secondly, the obviousness-type double patenting rejection in the present application, which holds claim 4 to be obvious over claims 28 and 29 in the '693 patent, renders the restriction requirement in the present application improper. The claims cannot be both obvious and patentably distinct, as such holdings are mutually exclusive.

Thirdly, in the context of the present invention, the application teaches that inflammatory cytokines, H_2O_2 and thrombin have a <u>common</u> mechanism of action in that they "increase aminophospholipid expression" and "induce the expression of aminophospholipids within the tumor vasculature" (see, *e.g.*, specification at page 33, lines 5-7; page 120; lines 5-9). Such teaching is supported by Example XIV of the specification, which provides actual data showing that H_2O_2 and thrombin induce phosphatidylserine expression at the surface of endothelial cells, which is correlated with the presence of inflammatory cells in the tumor environment. Moreover, the preliminary amendment submitted when the present application was filed

provided even further data showing that factors known to be present in the tumor microenvironment, including inflammatory cytokines, cause phosphatidylserine translocation to the surface of endothelial cells, which is also associated with a rise in intracellular Ca^{2+} (see, preliminary amendment and Exhibit E therewith).

Fourthly, and partly in light of evidence such as discussed above, further decisions of the Office are also contrary to the restriction requirement in the present application. For example, see U.S. Patent No. 6,783,760 ("the '760 patent"; Attorney Docket No. 3999.002399; **Exhibit A**), in which related combined cancer treatment claims have issued. In particular, the issued claims in the '760 patent recite administration of a therapeutic conjugate of an anti-aminophospholipid antibody and a second anti-cancer agent, where the second anti-cancer agents include chemotherapeutic agents listed in the same table as the present application[2] (claim 38), anti-angiogenic agents listed in the same table as the present application[2] (claim 42), inflammatory cytokines (claims 53 and 54), H_2O_2 and thrombin (claim 48) and calcium-flux inducing agents (claim 34, 51 and 52).

Therefore, based on scientific and procedural grounds, and on the decisions of the Office in related patents, all pending claims are drawn to an invention that is not properly subject to restriction and that is also in condition for allowance.

VI. Rejection of Claims 63 and 68 Under 35 U.S.C. § 112, Second Paragraph

Claims 63 and 68 are first rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. Although Applicants respectfully traverse, the Action's concerns are overcome.

[2]The tables of chemotherapeutic agents and anti-angiogenic agents in the '760 patent and the present application have different numbers, but the same content.

A. Claim 63

Claim 63 is rejected as the term "biologically effective time" is allegedly indefinite and the specification allegedly "does not provide a standard for ascertaining the requisite degree" (Action at page 5). In contrast, the specification provides detailed teaching on this point. For example, the specification teaches:

> "Alternatively, the at least a first anti-cancer agent may be administered to the animal or patient at a time sequential to the administration of the at least a first anti-aminophospholipid antibody, or antigen-binding fragment thereof. 'At a time sequential', as used herein, means 'staggered', such that the at least a first anti-cancer agent is administered to the animal or patient at a time distinct to the administration of the at least a first anti-aminophospholipid antibody. Generally, the two agents are administered at times effectively spaced apart to allow the two agents to exert their respective therapeutic effects, *i.e.*, they are administered at 'biologically effective time intervals'."
>
> Specification at page 32, lines 16-23.
>
> "To practice combined anti-tumor therapy, one would simply administer to an animal an anti-aminophospholipid antibody in combination with another anti-cancer agent in a manner effective to result in their combined anti-tumor actions within the animal. The agents would therefore be provided in amounts effective and for periods of time effective to result in their combined presence within the tumor vasculature and their combined actions in the tumor environment."
>
> Specification at page 119, lines 16-21.
>
> "In certain embodiments where the anti-cancer agent and anti-aminophospholipid antibody are applied separately to the animal, one would ensure that a significant period of time did not expire between the time of each delivery, such that the anti-cancer agent and anti-aminophospholipid antibody composition would still be able to exert an advantageously combined effect on the tumor."
>
> Specification from page 119, line 25 to page 120, line 1.
>
> "In some situations, it may even be desirable to extend the time period for treatment significantly, where several days (2, 3, 4, 5, 6 or 7), several weeks (1, 2, 3, 4, 5, 6, 7 or 8) or even several months (1, 2, 3, 4, 5, 6, 7 or 8) lapse between the respective administrations. This would be advantageous in circumstances where one treatment was intended to substantially destroy the tumor, such as the anti-aminophospholipid antibody treatment, and another treatment was intended to

prevent micrometastasis or tumor re-growth, such as the administration of an anti-angiogenic agent."

Specification at page 120, lines 21-27.

"It also is envisioned that more than one administration of either the anti-aminophospholipid antibody or the anti-cancer agent will be utilized. The anti-aminophospholipid antibodies and anti-cancer agents may be administered interchangeably, on alternate days or weeks; or a sequence of anti-aminophospholipid antibody treatment may be given, followed by a sequence of anti-cancer agent therapy. In any event, to achieve tumor regression using a combined therapy, all that is required is to deliver both agents in a combined amount effective to exert an anti-tumor effect, irrespective of the times for administration."

Specification at page 121, lines 1-7.

Accordingly, claim 63 is sufficiently definite as written. *Ex Parte Clarke*, 98 USPQ 195, 196 (P.O. Bd. 1953); *Application of Halleck*, 422 F.2d 911 (C.C.P.A 1970); *Revlon, Inc. v. Carson Products Co.*, 602 F.Supp 1071, 1098 (S.D.N.Y. 1985). Nonetheless, and without acquiescing with the present rejection in any way, claim 63 has been amended to remove the complained of language.

B. Claim 68

Claim 68 is rejected as the term "second therapeutic agent" is allegedly indefinite, the specification allegedly does not provide a standard for ascertaining the requisite degree and "one of ordinary skill in the art would not be reasonably apprised of the scope of the invention" (Action at page 5). The rejection is *prima facie* improper. Indeed, the Action itself evidences a clear understanding of the term "second therapeutic agent" in regard to both the present application and the patent issued from the parent application (Action bridging pages 5 and 6, particularly top of page 6).

In any event, "therapeutic agent" is being used according to its ordinary meaning as would be understood by those of skill in the art. That is, a remedial agent for the treatment of disease or disorders (Webster's collegiate dictionary). The specification does not suggest, let alone make clear, that "therapeutic agent" in claim 68 is intended be used in a manner different to its accustomed meaning. *ZMI Corp. v. Cardiac Resuscitator Corp.*, 6 USPQ 2d 1557 (Fed. Cir. 1988). There is nothing indefinite in the term "therapeutic agent" itself, and nothing in the specification to suggest anything other than its accustomed meaning, and claim 68 is thus *prima facie* definite. "Without an express intent to impart a novel meaning to claim terms, an inventor's claim terms take on their ordinary meaning." *York Prods., Inc. vs. Central Tractor Farm and Family Cent.*, 40 USPQ2d 1619, 1622 (Fed. Cir. 1996).

The § 112, second paragraph rejections are therefore overcome and should be withdrawn.

VII. Rejection of Claims 4, 6, 7, 49, 50 and 68 Under 35 U.S.C. § 103(a)

Claims 4, 6, 7, 49, 50 and 68 are rejected under 35 U.S.C. § 103(a) as allegedly being legally obvious over Fishman *et al.*, *Int. J. Oncol.*, 10:901-904, 1997 ("Fishman") in view of Tschmelitsch *et al.*, *Cancer Res.*, 57:2181-2186, 1997 ("Tschmelitsch"). Although Applicants respectfully traverse, the Action's concerns are overcome.

A. Claims 4, 6, 7, 49 and 50 are Allowed

As set forth above (**Section II**), Applicants appreciate the Action's determination that many claims are allowable (Action at summary page, and page 7). Without acquiescing with the present rejection in any way, Applicants first address the rejection by revising rejected claim 4 to incorporate the language of allowable claim 10, thus placing claim 4 into allowed form. As rejected claims 6, 7, 49 and 50 all directly or indirectly depend on claim 4, claims 4, 6, 7, 49

and 50 are all now in allowed form, based on the Action's determination that claim 10 is allowable.

B. Claims 68 and 82 are *Prima Facie* Allowable

The rejection of claims 4, 6, 7, 49 and 50 is overcome as set forth above. The § 103(a) rejection of the remaining rejected claim, claim 68, and new claim 82, which reflects unamended claim 4, is also overcome on various grounds.

The Action begins by stating that claim 4 (new claim 82) is drawn to "a method of treating an animal, comprising administering a therapeutically effective combination of at least a first monoclonal antibody or antigen-binding fragment thereof that binds to an aminophospholipid and at least a second chemotherapeutic agent or a compound that interferes with tubulin activity" (Action at page 6). Aside from unduly limiting the species of second therapeutic agent (see **Section V** in particular), the Action's statement includes one error and two important omissions of claimed features. The error is that claim 4 as then written (present claim 82) did not recite a "monoclonal" antibody, but "an antibody or antigen-binding fragment thereof".

Importantly, the Action's characterization of this claim includes two omissions of claimed features. More accurately, the claim is drawn to "a method of treating an animal <u>having a vascularized tumor</u>, comprising administering a therapeutically effective combination of at least a first antibody or antigen-binding fragment thereof that binds to an aminophospholipid <u>on the luminal surface of blood vessels of the vascularized tumor</u> and at least a second therapeutic agent, as defined in parts (a) to (e) of the claim (claim 82, emphasis added).

The Action has therefore read both the limitations "<u>vascularized</u> tumor" and "binds to an aminophospholipid <u>on the luminal surface of blood vessels of the vascularized tumor</u>" out of the

claims, which is prohibited by the law. Every element of a claim has meaning; the language of the claim as a whole must be considered and an interpretation should not be reached that renders a clause superfluous. *Genentech Inc. v. Chiron Corp.*, 42 USPQ2d 1608, 1612 (Fed. Cir. 1997). Claims should not be treated so as to improperly broaden the scope by 'reading out' limitations in claim language. *Lockheed Martin Corp. vs. Space Systems/Loral Inc.* 58 USPQ2d 1671 (Fed. Cir. 2001).

Fishman is cited as teaching the use of anti-phosphatidylserine (anti-PS) antibodies to treat melanoma (Action at page 6). Although it is not expressly stated, it appears from the Action at page 6 that the Office believes Fishman teaches all aspects of the claimed invention *other than* administering a second chemotherapeutic agent. This is not at all correct. When the present claim is properly interpreted, *i.e.*, as drawn to targeting aminophospholipids on the luminal surface of blood vessels of the vascularized tumor, it is clear that Fishman does not teach or suggest the claimed invention.

Fishman is limited to strategies aimed at binding malignant and cancer cells, including "malignant melanoma cells" (Fishman throughout, *e.g.*, abstract, introduction, Table 1, Figure 1, Figure 3). The presently claimed methods are directed to targeting the blood vessels of vascularized tumors, which are normal cells. Thus, Fishman does not teach or suggest all limitations of the claimed invention, and this fact alone is sufficient to overcome the § 103(a) rejection. As the Federal Circuit's predecessor held, "this court has stated that all limitations must be considered and that it is error to ignore specific limitations distinguishing over the references". *In re Boe*, 184 USPQ 38, 40 (CCPA 1974), citing *In re Saether*, 181 USPQ 35 (CCPA 1974); *In re Glass*, 176 USPQ 489 (CCPA 1973).

Moreover, Fishman teaches away from the claimed invention in important respects. In particular, Fishman teaches away from the claimed invention by consistently teaching that phosphatidylserine is not expressed at the surface of normal cells. For example, Fishman states "cancer cells differ from normal cells by the expression of phosphatidylserine (PS) on their outer membrane surface" (Fishman at abstract). In regard to normal cells, Fishman teaches "phosphatidylserine (PS) is localized exclusively in the inner leaflet of the cell membrane of normal cells" (Fishman in the legend to Figure 3; see also, abstract; page 903, column 1). Fishman continues, "the translocation of PS from the inner to the outer cell membrane is typical of tumor cells" (Fishman in the legend to Figure 3; text at page 903, column 1).

Thus, as the tumor vascular endothelial cells targeted by the presently claimed invention are normal cells, and as Fishman expressly and repeatedly teaches that phosphatidylserine is not expressed at the cell membrane of normal cells, but rather is "localized exclusively in the inner leaflet", Fishman clearly teaches away from the claimed invention. Such teaching away in the art is clear evidence of patentability. *Mendenhall v. Astec Industries, Inc.*, 13 USPQ 2d 1913, 1939 (Tenn. 1988), *aff'd*, 13 USPQ 2d 1956 (Fed. Cir. 1989).

Moreover, by concerning tumor cells, rather than tumor vasculature, Fishman is representative of the standard, but problematic prior art of tumor cell targeting, which is discussed in the background section of the present specification. For example, the specification teaches that both chemotherapeutics and immunotoxins against tumor cells are limited by tumor cell resistance, leading to antigen-negative or antigen-deficient tumor cells, which can survive and repopulate the tumor or lead to further metastases (specification at background). The poor accessibility of tumor cells is another limitation in therapies aimed at tumor cells. The specification teaches that the tumor mass is generally impermeable to molecules of the size of

antibodies and immunotoxins, such that the physical diffusion distances and the interstitial pressure within the tumor are significant limitations to therapies aimed at tumor cells (specification at background).

The present inventors developed vascular targeting methods for tumor treatment, at least in part, to overcome the many drawbacks associated with immunotoxins to cancer cells. "Recognition of need, and difficulties encountered by those skilled in the field, are classical indicia of unobviousness." *In re Dow Chemical Co.*, 5 USPQ 2d 1529 (Fed. Cir. 1988).

Fishman does not teach or suggest any aspect of tumor vasculature targeting, let alone targeting an aminophospholipid on the luminal surface of blood vessels of the vascularized tumor, as required by the presently claimed invention. Rather, Fishman generally represents the problematic prior art of tumor cell targeting and, in the context of phosphatidylserine, Fishman *teaches away* from the claimed invention by teaching that phosphatidylserine is <u>not</u> expressed by normal cells.

Presumably such facts were recognized by the Office during examination of the parent application, which issued as the '693 patent. Notably, Fishman is of record in the '693 patent and all claims were determined to be novel and non-obvious over Fishman (Fishman is cited on the face of the patent as the second reference under "other publications"). Applicants are aware that Fishman was not overtly discussed on the record in the '693 patent, but this supports Applicants' belief that the Office determined Fishman to be irrelevant to the invention as claimed. In any event, the present rejection is *prima facie* improper in light of the obviousness-type double-patenting rejection over the '693 patent. As the claims in the '693 patent are patentable over Fishman, and as the present claims are obviousness variations of the claims in the '693 patent, then the present claims are also patentable over Fishman.

C. Further Surprising Features of the Claimed Invention

As Fishman fails to teach or suggest the first part of the recited combination tumor treatment, claims 68 and 82 are *prima facie* patentable over Fishman, whether alone or in combination with Tschmelitsch. In any event, the claimed invention is a "combination" tumor treatment method, and further surprising features of the claimed invention over the cited art are evident in the claimed "combined treatment".

The Action admits that Fishman does not teach administration of anti-phosphatidylserine antibodies in combination with a chemotherapeutic agent (Action at page 6), a required feature of the claimed invention. The Action thus relies on Tschmelitsch in an attempt to cure the admitted deficiencies of Fishman. However, Tschmelitsch, even if properly combined with Fishman, not only fails to cure the deficiencies of Fishman, but itself further teaches away from the invention.

In the interest of efficiency, Applicants elect to address the combination of Fishman and Tschmelitsch. This is not an acquiescence that the proposed combination of Fishman and Tschmelitsch is legally proper; simply that there is compelling evidence that Fishman and Tschmelitsch, even if combined, fail to teach or suggest the claimed invention and, in fact, teach away from the invention.

It is first noted that Tschmelitsch suffers from one of the same fundamental defects as Fishman, in that neither teach nor suggest any aspect of targeting the blood vessels of a vascularized tumor, an important feature of claimed invention.

The Action cites Tschmelitsch as teaching an enhanced antitumor activity of combination radioimmunotherapy with chemotherapy in the form of 5-fluorouracil (5-FU). More particularly, the Action cites Tschmelitsch as teaching that mAb A33 alone showed no demonstrable effect on growth of established tumors, but that the combination of 5-FU and ^{131}I- mAb A33 resulted in

significantly higher antitumor activity (Action at page 6). Rather than rendering the claimed invention legally obvious, Tschmelitsch in fact provides further evidence of the surprising nature of the present invention.

Firstly, mAb A33 reacts with an antigen expressed by colon cancer cells (Tschmelitsch, *e.g.*, abstract). The report that mAb A33 alone shows no demonstrable effect on the growth of established tumors (Action at page 6; Tschmelitsch at page 2182) thus supports Applicants' position that methods of targeting tumor cells, known in general in the prior art, and to which both Fishman and Tschmelitsch are entirely limited, are largely ineffective (see, *e.g.*, specification at background). Fishman and Tschmelitsch do not teach or suggest or alternatives to tumor cell targeting, and particularly fail to teach or suggest targeting any component, let alone an aminophospholipid, expressed on the luminal surface of blood vessels of a vascularized tumor. The present invention thus already represents a surprising advance over Fishman and Tschmelitsch.

Secondly, Tschmelitsch uses the FB5 antibody, which binds to endosialin, a marker of human neovascular endothelium, as an isotype-matched negative control (Tschmelitsch at page 2181, column 2, last paragraph). The FB5 antibody binds to neovascular endothelium (present within the tumor vasculature) and yet has no anti-tumor effect, either alone or in combination therapy with 5-fluorouracil (Tschmelitsch throughout, *e.g.*, page 2182, column 2). This again highlights the surprising effectiveness of the anti-aminophospholipid antibodies of the present invention, which have marked anti-tumor effects, both alone (*e.g.*, the '693 patent) and in combination therapies. As explained in the specification, the present invention is based both on the surprising finding that aminophospholipids, such as phosphatidylserine and phosphatidylethanolamine, are accessible and stably targetable markers of tumor vasculature, and

on the unexpected discovery that naked antibodies against aminophospholipid components are capable of specifically inducing tumor blood vessel destruction and tumor necrosis *in vivo* (specification throughout, *e.g.*, first paragraph of Summary).

Thirdly, even using the chosen anti-tumor cell antibody (mAb A33), Tschmelitsch only observes an additive anti-tumor effect with a single agent, 5-fluorouracil (Tschmelitsch throughout, *e.g.*, page 2183). Notably, doxorubicin and carmustine[3] were tested in combination therapy with mAb A33 and found to be ineffective (Tschmelitsch throughout, *e.g.*, page 2183). Thus, rather than teaching the combination of immunotherapy and chemotherapy in general, as alleged in the Action at page 6, Tschmelitsch is confined to showing the combined use of mAb A33 and 5-fluorouracil in colon cancer. Even the additive anti-tumor effect observed with this single agent may be more connected with the particular agent and disease chosen, as 5-fluorouracil is taught to be the "mainstay of treatment" for colon cancer (Tschmelitsch at introduction, second paragraph).

Whatever the reason, the failure of doxorubicin and carmustine combinations to improve therapy simply cannot be ignored. Therefore, rather than supporting the rejection, Tschmelitsch thus represents long felt, but unsolved needs and the failure of others, long held to be indicia of nonobviousness. *Graham v. John Deere Co.*, 148 USPQ 459 (U.S.S.Ct. 1966).

Thus, the § 103(a) rejection over Fishman in combination and Tschmelitsch is improper and overcome. As a proper *prima facie* rejection has not been established, Applicants have no burden to show any evidence of unexpected results for the claimed invention. The Board of Patent Appeals and Interferences has clearly stated:

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[3]The combined use of carmustine, which failed in Tschmelitsch, is specifically recited in claim 50.

> "The burden of establishing a *prima facia* case of obviousness falls upon the Examiner. Therefore, the evidence upon which the Examiner relies must clearly indicate that a worker of routine skill in the art would view the claimed invention as being obvious, as meant by 35 U.S.C. § 103."
>
> *Ex parte Wolters and Kuypers*, 214 USPQ 735 (PTO Bd. App. 1979); emphasis added.

Fishman and Tschmelitsch, with their many irrelevancies, teaching away and overt failures, clearly do not indicate that a worker of routine skill in the art would view the claimed invention as being obvious, as meant by 35 U.S.C. § 103. Nonetheless, Applicants elect to volunteer further evidence showing the surprising effectiveness of a combination therapy of the invention. **Exhibit B** presents data demonstrating that combination tumor treatment using an antibody that binds to an aminophospholipid (3G4 antibody) and the chemotherapeutic drug, docetaxel, produce synergistic effects. As taught in the specification, these agents are designed to attack the tumor vasculature endothelial cell and tumor cell compartments, respectively leading to synergistic treatment with lower toxicity. The results show that this combination therapy did indeed significantly enhanced treatment efficacy.

The § 103(a) rejection of all claims is therefore overcome and should be withdrawn.

VIII. Specification

The informalities in the specification noted in the Action at page 4 have been corrected by amendment.

IX. Conclusion

This is a complete response to the referenced Official Action. In conclusion, Applicants submit that, in light of the foregoing remarks, the present claims are drawn to an invention that is not properly subject to restriction and that is in condition for allowance. Should Examiner

Fetterolf have any questions or comments, a telephone call to the undersigned Applicant's representative is earnestly solicited.

Respectfully submitted,
Williams, Morgan & Amerson, P.C.
Customer No. 23720

Shelley P.M. Fussey, Ph.D.
Reg. No. 39,458
Agent for Applicants

10333 Richmond, Suite 1100
Houston, Texas, 77042
(713) 934-4079

Date: December 8, 2004

EXHIBIT B

Synergistic Tumor Treatment in Combined Therapy

The following data demonstrate that combination tumor treatment using an antibody that binds to an aminophospholipid (3G4 antibody) and the chemotherapeutic drug, docetaxel, produce synergistic effects. As taught in the specification, these agents are designed to attack tumor vasculature endothelial cell and tumor cell compartments, leading to synergistic treatment with lower toxicity. The results show that this combination therapy did indeed significantly enhanced treatment efficacy.

The anti-tumor effect of the combined therapy of 3G4 with docetaxel was examined in an orthotopic model in SCID mice bearing human MDA-MB-435 breast carcinoma. Mice bearing orthotopic MDA-MB-435 human breast tumor were treated i.p. with 3G4 alone (100 μg/dose), docetaxel alone (10 mg/kg), or 3G4 in combination with docetaxel (100 μg/dose and 10 mg/kg, respectively), for three weeks, with administration 3 times a week. Treatment started 6 days after tumor cell implantation.

These studies showed that the combined therapy of 3G4 plus docetaxel resulted in growth inhibition of 90%. Growth inhibition of 3G4 plus docetaxel was significantly superior to 3G4 alone ($p<0.005$) and docetaxel alone ($p<0.01$). Thus, clear synergy results from this combined treatment.